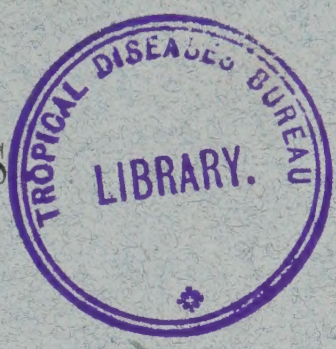


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AN ADDRESS

ON THE

RECENT ADVANCES IN THE KNOW-
LEDGE OF MALARIA

BY

PATRICK MANSON, M.D., LL.D., F.R.C.P., F.R.S.

[From Volume 84 of the 'Medico-Chirurgical Transactions']

LONDON

PUBLISHED BY THE ROYAL MEDICAL AND CHIRURGICAL SOCIETY
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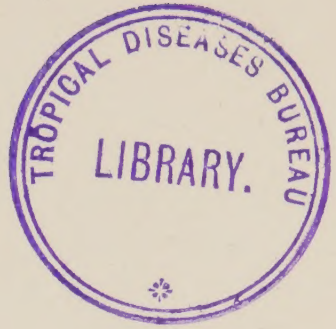
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WHEN the subject of the malaria parasite was last before the Society, Golgi's views as to the fever or intracorporeal cycle had already been generally accepted. There remained, however, many other forms of the parasite as seen in the blood, which were not included in Golgi's cycle, and which up to that time had not received adequate explanation, notably the crescent form, the large free spherical forms, the flagellated bodies, the free flagella, etc. These were by many, especially by the Italians and their followers, regarded as effete, moribund, "agony," or degeneration forms, on the very inadequate ground that their nature and purpose were not apparent, and because, up to that time, no nucleus had been demonstrated in such parasitic elements. The view had been

¹ Being remarks introducing Dr. L. Sambon's Report on Experiments in London and the Roman Campagna, presented at the meeting of the Royal Medical and Chirurgical Society, January 8th, 1901.

advanced by some of us that these so-called degeneration forms, because certain of them were not evolved until the blood containing them had left the human body, really belonged to the hitherto unrecognised extra-corporeal cycle of the parasite; and because, while in the human body they were still enclosed in red blood-corpuscles and therefore could not escape in virtue of their own efforts, that they must be abstracted and nursed, so to speak, by some suctorial animal, which, from geographical and epidemiological reasons, we considered to be the mosquito; further, because malaria did not occur in every place where there were mosquitoes, that the malaria parasite must be subserved by a particular kind of mosquito. The complete proof of this hypothesis was supplied by Ross both as regards bird and human malaria. Important supplementary evidence was forthcoming in MacCallum's interesting observations on the fertilisation of the female gamete in the case of halteridium, an analogous parasite of certain birds. Ross's observations have now been fully confirmed by the Italians, by Daniels, by Koch, and others. Experimental proof has also been given. Grassi, Bignami, and Bastianelli have recently succeeded in experimentally conveying, by means of mosquito bite, the malaria parasite from one human being to another, just as Ross had previously done in the case of the proteosoma-malaria parasite of the sparrow.

In consequence of these observations our knowledge of the malaria parasite is now so complete that we can indicate with a fair amount of precision its exact zoological position. Recent observation has shown that its place in Nature is alongside the coccidia, that its human phase corresponds to what was formerly known as the eimeria stage of these organisms, its mosquito phase to the coccidial stage. The diagram represents in comparison the life cycles of *Coccidium Schubergi* and of *Hæmomenas præcox*—the name applied by Ross to the parasite of tropical malaria. The escape of the sporozoite from the oocyst or zygote and, in the case of the coccidium,

its entrance into an epithelial cell, in the case of the malarial parasite its entrance into the blood-corpuscle, is practically the same as regards both parasites. The succeeding figures show the formation of the schizont; the multiplication of nuclei; the formation of merozoites; the breaking up of the ripe parasite; and, finally, the divergent development of the various merozoites or spores, some entering the epithelial cell in the case of the coccidium, or blood-corpuscle in the case of the malaria parasite and renewing the schizont cycle, others becoming converted into macrogametes, others again into microgametes. In both types of parasite we see that the formation of microgamete and macrogamete is conducted on exactly similar lines; in both we see the fecundation of the macrogamete by the entrance into it of the microgamete, the fusion of nuclei,—male and female, the encapsulation, the formation of the oocyst in the case of the coccidium and the zygote, as it has been termed, in the case of the malaria parasite. At this point, however, the method of development in the two organisms diverges—changes to a certain extent; whereas in coccidium the nucleus divides into four and four sporocysts are formed in the interior of each of which two sporozoites are subsequently developed; in the case of the malaria parasite the division of the nucleus is much more elaborate, the fragments becoming surrounded by protoplasm on the surface of which a vast number of sporozoites are ultimately formed. With this exception the development of coccidium and that of the malaria parasite correspond in every particular.

Ray Lankester has lately drawn attention to a singular circumstance, one which might be regarded from the biologist's point of view as an abnormality, in the evolution of the malaria parasite. In the foregoing description there is distinct evidence of parthenogenesis. Ray Lankester points to the characters of the microgamete and of the sporozoite as indications that it is conducted by what appears to be a male element, and not, as is usual, by a female element.

Unfortunately, from multiplication of terms much confusion has crept into the nomenclature of the various phases of the evolution of the malaria parasite. It is highly desirable that a reform in this respect should be instituted. It would be well that some agreement be arrived at on this subject.

Although we now know a great deal about the life-history of the parasite, much is still required to round off this knowledge. We would like to be able to say what are the circumstances which determine the destination of the merozoite, or spore; what it is that determines one of them to enter on the endogenous cycle and carry on the life of the parasite in man, and what it is that determines another to assume the characters of a macrogamete, and what it is that determines a third to take on the characters of a microgamete and provide for the exogenous cycle in the mosquito. We know nothing of the latent phase of the parasite further than that there must be such a phase; we know that malarial infections may remain latent in the human body for months, and even years; that an infection contracted in India, for instance, without showing any clinical evidence of its presence there, may, months subsequently, become active for the first time when the patient has returned to England where, perhaps, he may get his first attack of ague whilst walking down Regent Street.

Another important point calls for settlement. Is man the only vertebrate host of the malaria parasite, or, like many other parasites, has it a variety of hosts? Among the nematodes such a multiplicity of hosts is common: *Trichina spiralis*, e. g. can live in rats, pigs, dogs, men, and many other vertebrates; among the protozoa, *Trypanosoma Evansi*, e. g. occurs in dogs, horses, donkeys, cattle, and other beasts. Why not a similar multiplicity in the case of the malaria parasite? Indeed, there are some indications that such may be the case. Dionisi's recent discovery of several species of intra-corpuseular parasites in the bat, closely resembling those of man, is extremely

suggestive; all the more so seeing that the bat, like primitive man, is a cave-dweller, a troglodyte, and even accompanies him when in process of civilisation he takes to building himself a house.

Another singular feature about malarial infection is dimly indicated by recent observations in Africa as well as in Italy. Drs. Stevens and Christophers tell us that they have rarely found crescent bodies in the blood either of Europeans or of natives in Africa. Daniels, for British Central Africa, and Plehu, for Camaroon, bear similar testimony. Now I can vouch that the crescent body is exceedingly common in such patients when they come to England. At the present moment I have under observation at the Seamen's Hospital four malarials, Europeans, all of whom contracted their fever on the Niger, in whose blood the crescent parasite is present in great abundance. I constantly see similar cases. Are we to suppose that if these four men had remained in West Africa the crescent form of the parasite would not have developed, that it was only in consequence of their having left West Africa and come to a more temperate climate that this phase of the parasite was evolved? Drs. Christophers and Stevens tell us that the gamete form in West Africa, in the case of the tropical parasite, is almost invariably a non-crescentic parasite, being a simple pigmented disc of protoplasm, closely resembling the intra-corpuscular forms of the ordinary quartan parasite. This reluctance, so to speak, of the African parasite to form crescents in its native country apparently is not shared by the corresponding Indian parasite. Ross and others speak freely of this phase as occurring in India. Is the African parasite specifically different from the Indian, and, if so, why should it take to forming crescents when it comes to England? It is to be regretted that the recent expeditions to Africa for the study of malaria did not give more attention to this point.

We know now that the mosquito is the definitive host of the malaria parasite. So far it has been found only in

members of the genus *Anopheles*, of which there are at least forty-six species. Of these *A. funestios*, *A. costalis*, *A. claviger*, *A. pseudopictus*, *A. superpictus*, and *A. bifurcatus* have been incriminated; but how many more of the remaining forty odd are capable of subserving the parasite we do not know. Of the two hundred and fifty known species of *Culex*, *C. mimeticus*, *C. pipiens*, *C. tæniatus*, *C. nemorosus*, *C. malarix*, and three unidentified species experimented with by Daniels in British Central Africa, have alone been tested and found inhospitable as regards malaria, but it is quite possible that some of the other *Culices* may be efficient hosts.

The distribution of malaria having been found to depend upon the distribution of certain species of mosquitoes, it is of importance, from a practical point of view, to ascertain on what the distribution of these mosquitoes depends. The study of this point must be approached from two directions. We must study the circumstances favourable to any species that may be investigated, and we must also study the circumstances which are unfavourable to such; more especially the latter, for it is quite possible that having ascertained the inimical conditions we may be able to reproduce them, and so have at our command means to destroy the dangerous mosquitoes. Studies in this latter line have not been instituted as yet, although they are in contemplation.

Much attention has been bestowed upon what is generally supposed to be a phase of malarial intoxication, viz. black-water fever. One German and two English expeditions have made it a subject of special investigation. So far, the practical results have been *nil*, although much useful information has been acquired bearing both on black-water fever and on malaria. It has been ascertained that the geographical range of black-water is more extensive than is generally supposed. Many theories have been advanced as to its nature and causation; for example, the old idea, first promulgated by the Italians, that it is an expression of quinine poisoning,

has been brought prominently forward by Koch. Whatever may be the rôle of quinine as a subsidiary cause it is certainly not *the* cause of black-water fever, for of late many instances of the disease have been recorded in individuals who have never taken quinine. It has also been stated that black-water fever is an intense form of malaria, whatever that may mean; if it means that it is a high degree of infection, that is, the result of a phenomenally abundant swarm of malaria parasites in the blood, the idea is certainly untenable, for in many cases of black-water fever the malaria parasite is absent, and in cases in which the patients have come to the post-mortem table, although some evidence of malarial infection is obtainable in nearly every case, in many instances the evidence is only that of a mild infection as regards abundance of parasites. Again, black-water fever is notoriously absent from many intensely malarial places, the Roman Campagna for example. One important test for malarial infection black-water fever does not respond to; it is not amenable to quinine. Another theory of its causation attributes it to malarial cachexia; this, too, is untenable, for black-water has been known to occur in individuals within a few weeks of their arrival in the endemic zone; in other cases there has been complete absence of the usual evidences of cachexia before the development of the black-water symptoms. One theory with a good deal in its favour is to the effect that black-water is the result of a specifically distinct type of malaria parasite; another that it is the result of ordinary malarial infection, the virulence of the parasite having been increased by transmission through a particular but undetermined species of mosquito; yet another theory is that black-water fever is a disease *sui generis*, with its special but as yet undiscovered parasite. This last view has much in its favour. The peculiar geographical limitation of the disease, its seasonal prevalence, the almost complete immunity of native races, all favour this idea. In these and other respects it seems to be on all

fours with the Texas fever (hæmoglobinuric) of cattle. We know that cattle bred within the endemic area of this disease rarely exhibit the specific symptoms, but that cattle coming from an immune district on entering the endemic area are readily attacked. This is exactly what happens in regard to black-water; the native African is hardly ever affected, whereas the European coming from outside the endemic area is frequently affected. The connection of black-water fever with the malaria parasite seems to have received a parallel in Edington's observations in cattle salted to Texas fever. This talented observer found that such cattle, although originally free from the symptoms of Texas fever, when inoculated with rinderpest frequently developed hæmoglobinuria and exhibited in their blood the parasite (*Pirosoma bigeminum*) of Texas fever. It may be, therefore, that the malaria parasite takes the place in the development of black-water in man that the rinderpest infection in the case of Edington's experiments took in the determination of black-water in cattle.

Hill showed that out of 45 deaths from malaria in Georgetown, British Guiana, from June, 1893, to June, 1895, in persons born in the colony, 31 were under 13 years of age, and only 3 over 21, and in two of the latter the evidence was only clinical. Daniels, in a long series of post mortems from 1893 to 1895, also made in Georgetown, British Guiana, showed that in the series 1289 were born in the colony, or were from other malarial countries. In these 1289 post mortems, pigment (malarial) was found in none under a month old, but was present in those over a month and under 12 months in 25 per cent.; over 1 year and under 2 in 54·5 per cent.; over 2 years and under 5 in 81·4 per cent.; whilst above 30 it was found only in 17·9, 14·1, 13·2, 11·1, and 11·6 per cent., that is decreasingly in each ascending decade respectively. He also noted that after 20 the pigment is very rarely recent in appearance, and after 30, with one or two exceptions, that it is obviously very old. The conclusion

was drawn by Daniels that immunity is acquired by a class in this malarious district in the course of exposure for some 20 years to the infection and, from evidence based on its relative frequency—evidence persisting for considerable periods, in some cases for years,—that this immunity is probably acquired through previous attacks.

What Daniels first proved from observations on a product of the parasite, long afterwards Koch, Christophers and Stevens proved from observations on the parasite itself. They have shown that in the endemic area of malaria practically all native children harbour the parasite. Native children, therefore, are an especially important source of infection. The practical interference therefrom is, that in malarial countries native houses and villages should be carefully avoided.

The most valuable outcome of the recent discoveries in the ætiology of malaria is the enormous power they place in our hands in regard to the prophylaxis of this disease. As the mosquito is a necessary element in the cycle of the parasite, it is manifest that if there are no mosquitoes there will be no malaria; therefore, wherever practicable, mosquitoes should be destroyed. This can be done to a limited or to a considerable extent according to circumstances, at all events in settled districts, by draining, or filling in, or poisoning all such collections of water as the mosquitoes frequent. As the parasite is introduced into man by the bite of the mosquitoes, it is evident that if this bite were avoided malaria would never be contracted; therefore it is of importance to advise and to use means for protecting the human body from the bites of these insects. Then, as quinine kills the parasite, or rather represses it, in the human body, wherever practicable it is advisable to keep the source of the infection of the mosquito at bay by the free use of this drug. In practice some of these measures will be found applicable in one place and some in another. It would be unwise to give general rules for every place; local circumstances must determine which method or methods

of prophylaxis are especially suitable and should be employed. It must be borne in mind that although complete protection everywhere and to every case may be impracticable, relative protection is always possible, should be attempted, and must be of immense value. It is evident, for example, that if in a given district only one mosquito in a thousand is infected with the malaria parasite, and that if in this district a man allows himself to be bitten, say through carelessness in the use of mosquito nets, by ten mosquitoes each night, in the course of a year he will be bitten from three to four times by infected insects. He will therefore be liable every year to frequent reinfection. Whereas if the same man, by exercising a fair amount of care, reduced the number of bites to one a week, he would be bitten by only fifty-two mosquitoes in the year, the probability being that none of these is infected; so that he might pass ten, twenty, or even thirty years in a malarial country before he contracted the disease. Relative protection as against malaria is therefore of immense value, just as is that afforded by vaccination against smallpox, or a good water-supply against typhoid.

As a contribution to popularising the knowledge now acquired that malaria is conveyed by the mosquito, and that it can be prevented by simple methods, methods that are quite compatible with active life, the experiments about to be described by Dr. Sambon were devised. It is right to mention that these experiments were rendered possible only by the intelligent appreciation of the possibilities of modern medicine, and of its importance as a factor in colonial development, by Mr. Chamberlain.



DESCRIPTION OF PLATE XXII.

On Recent Advances in the Knowledge of Malaria (Dr. Patrick Manson).

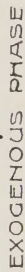
FIG. 1.

Development of *Coccidium schubergi*.—1. Sporozoit enters epithelial cell and commences the asexual, eimeria, or endogenous cycle. 2 and 3. Development of the schizont. 4. Multiplication of nuclei. 5. Daughter-nuclei arrange themselves at the periphery of the schizont. 6. Formation of merozoits. 7♀ and 7♂. Female and male merozoits entering fresh epithelial cells, 8, and commencing the sexual, exogenous, or coccidium cycle. 7b. Merozoit destined for the renewal of the endogenous or eimeria cycle. 9 and 10. Development of the female (macrogamete) and male (microgamete) gametes. 11. Maturation of the macrogamete by expulsion of caryosome. 12. Multiplication of nuclei and their peripheral arrangement in the microgamete. 14. Development of microgamete. 13. Fertilisation of macrogamete. 15. Fusion of male and female nuclei, encapsulation and formation of oocyst. 16 and 17. Division of nucleus. 18. Formation of four sporocysts. 19. Formation of two sporozoits in each sporocyst. 20. Sporozoit on its way to enter epithelial cell and renew endogenous cycle.

FIG. 2.

Development of *Hæmomenas præcox*.—a. Blood-corpuscle into which a spore or a sporozoit has just entered and commenced the endogenous cycle in man. b and c. Growth and pigmentation of the amœbula in the blood-corpuscle. d. Formation of sporocyte. d¹ and d². Female and male spores about to enter blood-corpuscles in preparation for the exogenous, sexual phase in the mosquito. d³. Spore destined to enter blood-corpuscle and renew the human or endogenous phase. e and f. Female and male gametes in blood-corpuscles; they have assumed the crescent shape and await ingestion by the mosquito. g. Female gamete (macrogametocyte) having been ingested by the mosquito has assumed the spherical form. h. Male gametocyte, after ingestion by the mosquito, has projected microgametes, j, which, breaking away, impregnate the female gamete, i. k. Zygote (fertilised macrogamete) on its way to the stomach wall of the mosquito—"travelling vermicule" stage. l. Encapsulation of zygote in stomach wall of mosquito, and formation of zygotomeres. m. Formation of sporozoits or blasts on surface of zygotomeres. n. Rupture of capsule and escape of sporozoits into mosquito's body cavity. o. Sporozoits on their way to human blood-corpuscles *viâ* the mosquito's salivary gland and proboscis.

Fig. 1.



(ÆSTIVO-AUTUMNAL FEVER)

